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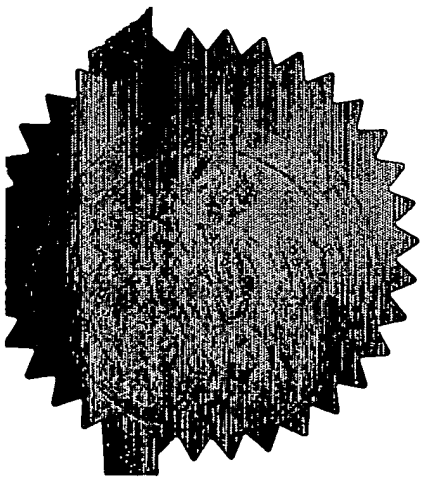

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Dated 28 June 2004

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18JUN03 E815999-1 D10032
P01/7700 0.00-0314149.6

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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Cardiff Road
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1. Your reference OLA/PDJ/1

2. Patent application number *(The Patent Office will fill in this part)* 0314149.6

18 JUN 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GENERICS [UK] Ltd.,
Albany Gate,
Darkes Lane,
Potters Bar, Herts.,
EN6 1AG

Patents ADP number *(if you know it)* 81187470001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Novel Amorphous Forms

5. Name of your agent *(if you have one)* Private Applicant

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

DR PAUL JENKINS
(Address as above)

Patents ADP number *(if you know it)* 84658660001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
	N/A		

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*
	N/A	

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

[redacted]er the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	5
Claim *(s)*	1
Abstract	1
Drawing *(s)*	2 + 2

10. If you are also filing any of the following, state how many against each item.

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	1
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

Signature P.D. Jenkins Date 17/6/02

12. Name and daytime telephone number of person to contact in the United Kingdom Dr PAUL JENKINS 01707 853249

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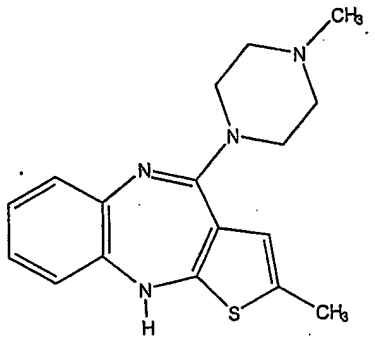
NOVEL AMORPHOUS FORMS

DESCRIPTION

The present invention relates to novel amorphous forms of the antipsychotic drug olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (I), processes for preparing such forms, compositions comprising such forms, and uses for such forms and compositions.



I

The manufacturing process for many pharmaceuticals is hindered by the fact that the organic compound which is the active drug substance has an irregular crystalline form. In some cases, such irregularities can cause handling difficulties during the manufacturing process and/or undesirable properties being imparted to the final drug or dosage form. The latter include inconsistent drug substance dissolution rates and the like.

Olanzapine was originally described as a metastable crystalline product, referred to in patent US 5736541 as Form I, wherein a more stable crystalline form, referred to as Form II was also disclosed. Crystalline alcohol solvates of olanzapine have also been disclosed in patent US 5703232 and further crystalline forms of olanzapine,

referred to Forms III, IV and V respectively have been disclosed in patent US 6348458.

Difficulties may ensue if the pharmaceutical material contains mixtures of polymorphs, especially if the different polymorphs have varying physical properties. An amorphous form of a drug may have the particular advantages of *inter alia* a) having improved bio-efficacy as a result of the higher solubility and dissolution rate *etc* or b) being overall more constant in polymorphic form.

It has been surprisingly found that olanzapine has an amorphous form for which the glass transition temperature (Tg) is ~66°C. As this temperature is so high, it would suggest that when the new material is stored way below this temperature (for example 25°C) the kinetics of converting to the stable crystalline form may be slow, and an amorphous phase may be stable during the shelf life of the product. Consequently the amorphous form of the present invention will be suitable to use as a pharmaceutical and have the advantages over the crystalline forms described earlier.

It is an object of the present invention to provide olanzapine in a solid amorphous form that affords the compound improved handling properties and/or improved properties as a pharmaceutical agent.

Therefore, a first aspect of the present invention is an amorphous form of olanzapine.

The amorphous forms in accordance with the invention can be used to advantage in the preparation of pharmaceutical dosage or drug forms. When in particulate form, the amorphous form in accordance with the invention is free flowing and does not present any of the handling difficulties associated with irregularly shaped crystals. It, therefore, can be employed in the manufacture of pharmaceuticals that do not suffer from the problems, such as inconsistent drug substance dissolution rates and the like, that can be manifest in dosage forms manufactured using previously

available forms of Olanzapine that have irregularly shaped and/or metastable crystals.

A further aspect of the present invention provides a process for the preparation of an amorphous form of Olanzapine comprising melting one or more crystalline forms of olanzapine, preferably comprising the further step of cooling of the melt.

Accordingly, in further aspects, the present invention provides a method of preparing a pharmaceutical dosage form that utilises an amorphous form in accordance with the first aspect of the invention. It also provides a pharmaceutical dosage form prepared or preparable by such a method. The dosage form is preferably solid and in addition to one or more conventional pharmaceutically acceptable excipient(s). Preferred dosage forms in accordance with the invention include tablets, capsules and the like. Tablets can be prepared by conventional techniques, including direct compression, wet granulation and dry granulation. Capsules are generally formed from a hard gelatine material and can include a conventionally prepared granulate of excipients and adduct or solvate in accordance with the invention.

The amorphous forms in accordance with the invention may also be useful as precursors to other novel polymorphic forms of Olanzapine that may be useful in the preparation of pharmaceutical products.

In a further aspect of the invention, there is provided the use of the form in accordance with the first aspect of the invention for the preparation of a medicament, preferably for use in treating psychiatric illnesses, such as psychoses.

The present invention is illustrated but in no way limited by the following example and figures.

Brief description of Figures

Figure One: IR spectra of amorphous olanzapine

Figure Two: XRPD spectrum of amorphous olanzapine

Figure Three: DSC trace of amorphous olanzapine

Differential Scanning Calorimetry was performed on a Mettler Toledo 821e.

Infra Red analysis was performed on a Bruker Equinox 55 using a specac diamond ATR system between 4000 cm^{-1} and 550 cm^{-1}.

XRPD was performed on a Brukers D8 advance difractometer, at 25°C between the angles of 4° and 50° 2 theta.

Karl Fischer analysis was performed using Mettler Toledo DL53 under standard conditions.

Example One

Crystalline olanzapine (6.80g) was weighed into a beaker and placed into an oven at 203°C to melt. After 45 minutes the molten olanzapine was poured into a dish to form a brittle block. The sample was then allowed to cool at room temperature for 3 hours.

The sample was ground in a clay mortar and pestle and analysed by IR (Figure One), XRPD (Figure Two) and DSC (Figure Three).

DSC analysis of the sample indicates that the sample was amorphous.

Karl Fischer analysis also indicated that the sample contained no water and was not a hydrated form.

The sample of ground olanzapine was stored at room temperature for 13 weeks for stability testing using XRPD analysis.

When exposing X-rays to a sample that is in an ordered crystalline lattice then a series of diffraction lines giving a characteristic "finger print" for that lattice. This is the main technique to compare different crystalline polymorphic forms of a

compound. However, if the sample is completely in an amorphous state (i.e. not in a regular lattice) then no such diffraction lines will be observed, and a very diffuse broad band will be observed relating to scattering of X-rays from the sample.

Figure Two shows the XRPD pattern for the sample prepared in Example One and no diffraction is observed, with just a broad diffuse band indicating the sample is in an amorphous form. No difference was observed in spectral analysis of the original sample and on a sample that had been kept in storage for 13 weeks at room temperature.

It can be concluded that by the melting of crystalline olanzapine and subsequent cooling that an amorphous phase can be formed. Due to the surprisingly relatively high Tg of ~66°C, nucleation and crystallisation is slow and not observed even after coarse grinding and prolonged storage.

Claims

1. An amorphous form of Olanzapine

2. An amorphous form of Olanzapine with an IR spectrum substantially as shown in Figure One

3. A process for the preparation of an amorphous form of Olanzapine comprising melting one or more crystalline forms of olanzapine.

4. A process for the preparation of an amorphous form of Olanzapine as characterised in claim 4, further comprising the step of cooling the melt.

5. A pharmaceutical composition comprising an amorphous form of Olanzapine as claimed in any of claims 1-2

6. The use the pharmaceutical composition as claimed in claim 6 for the preparation of a medicament for the treatment of a psychiatric illness

7. The use of claim 7 when the illness is psychoses.

Abstract

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Novel Amorphous Forms

An amorphous form of Olanzapine and a process for its preparation.

Figure One: IR spectra of amorphous olanzapine

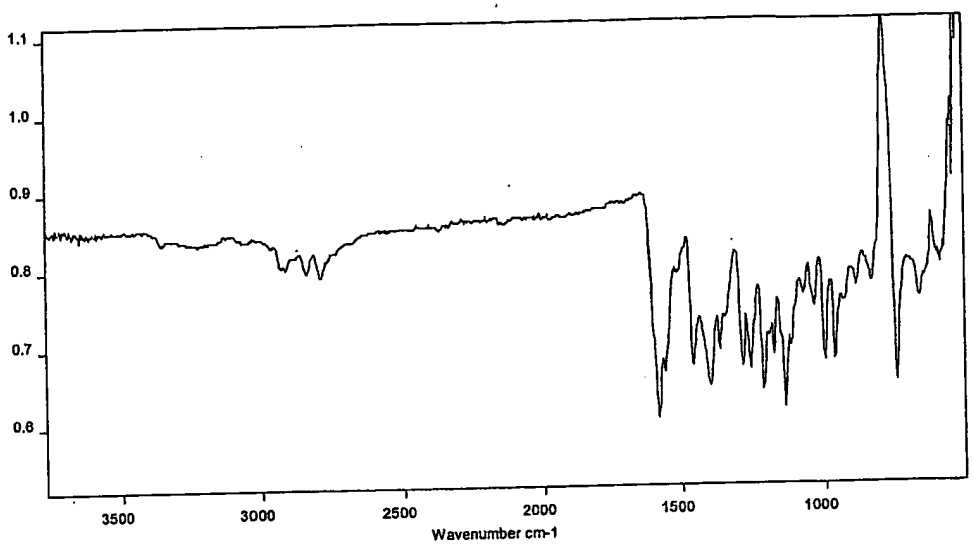

Figure Two: XRPD spectrum of amorphous olanzapine

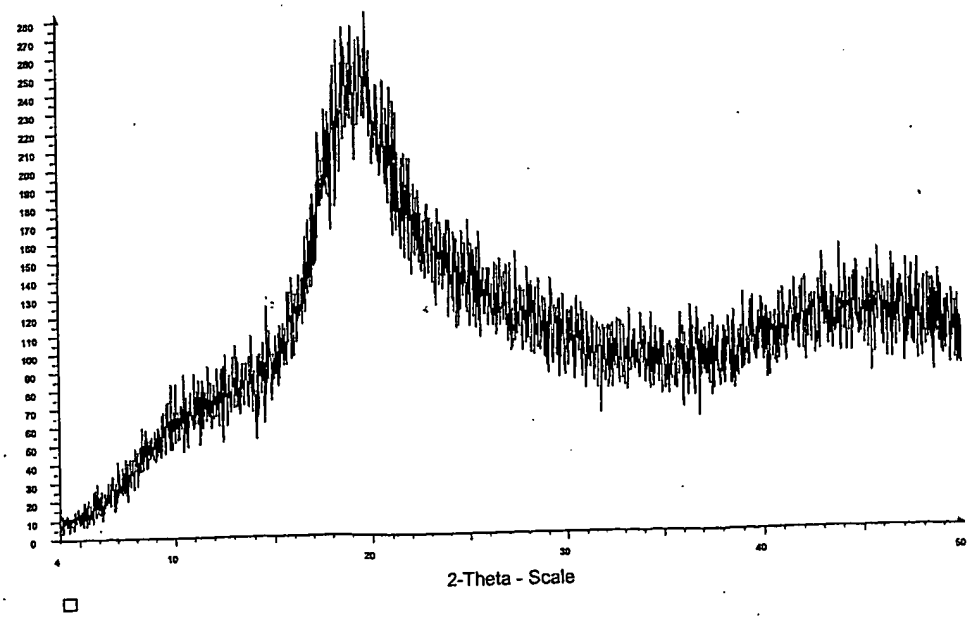

Figure Three: DSC Trace of amorphous olanzapine